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Infections Caused by *Klebsiella ozaenae*: a Changing Disease Spectrum

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A total of 64 isolates of *Klebsiella ozaenae* were recovered from 36 patients during a 40-month period. Over 7,500 isolates of *K. pneumoniae* were isolated during the same time period. Before this decade, *K. ozaenae* was considered to be only a colonizer of the nasopharynx or a putative cause of ozena (atrophic rhinitis). *K. ozaenae* was recovered most frequently from sputum in mixed culture but was associated with infection in 12 patients (2 with bacteremia, 3 with urinary tract infection, 1 with soft tissue infection, and 6 with mucopurulent nasal discharge). The spectrum of disease caused by this organism is more extensive than has been appreciated previously.

Klebsiella ozaenae has seldom been isolated from serious infections. It has been described primarily as a colonizer of the oral and nasopharyngeal mucosa or in association with ozena (atrophic rhinitis) (1-3, 9, 11, 13). Recently, the isolation of *K. ozaenae* from blood has been reported (1).

From January 1974 to May 1977, there were 64 clinical isolates of *K. ozaenae* from 35 different patients at the University of California, Los Angeles (UCLA) Medical Center and one patient at the Veterans Administration (VA) Wadsworth Hospital Center; these included two instances of bacteremia. In this paper, we describe our experience with infections caused by *K. ozaenae* and discuss the bacteriology and pathogenic potential of this organism.

MATERIALS AND METHODS

The records of the Anaerobic Bacteriology Laboratory of the VA Wadsworth Hospital Center and the Bacteriology Laboratory of the UCLA Medical Center from January 1974 through May 1977 were reviewed for all isolates of *K. ozaenae*. The records of all patients from whom *K. ozaenae* was isolated were also reviewed. Infection associated with *K. ozaenae* was considered to be present if the patient(s): (i) were febrile and were bacteremic with *K. ozaenae*, (ii) had fever, pyuria, dysuria, or urinary frequency and $\geq 10^5$ colony-forming units (CFU) of *K. ozaenae* per ml in a urine culture, (iii) had either a cellulitis or purulent drainage from which *K. ozaenae* was cultured, or (iv) had a mucopurulent nasal discharge from which *K. ozaenae* was isolated.

Bacteriology. All organisms were isolated and identified as *K. ozaenae* by established morphological and biochemical criteria (6; Table 1). In addition, isolates were also identified by the use of the API 20E System (Analytabs Products, Inc., Plainview, N.Y.). Antimicrobial susceptibility testing was performed by the World Health Organization-International Collaborative Study agar dilution method (5). Isolates were considered to be susceptible if the minimal inhibitory concentrations of the following drugs were (micrograms per milliliter): ampicillin, ≤ 16; tetracycline, ≤ 4; cephalothin, ≤ 16; chloramphenicol, ≤ 8; gentamicin, ≤ 8; tobramycin, ≤ 8; kanamycin, ≤ 16; and amikacin, ≤ 16.

RESULTS

Bacteriology. The anticipated biotypes of *K. ozaenae* and *K. pneumoniae* are included in Table 1 and are compared to the biotypes of our isolates of *K. ozaenae* (one isolate per patient).

Selected case reports (see Table 2): Case 1 (bacteremia and mastoiditis). A 52-year-old white male with alcoholic liver disease, ascites, diabetes mellitus, and hypertension was admitted to the VA Wadsworth Hospital Center with symptoms of fever and confusion. One month before admission, he fell on his left side, hitting his skull and ear. Three days later, he developed a clear discharge from the left ear which became purulent. Three days before admission, the patient developed fever and shaking chills.

Physical examination revealed a rectal temperature of 39.7°C; pulse, 110; respiratory rate, 20; and blood pressure, 150/100 mm of Hg. The patient was lethargic but responsive. His neck was freely movable. There was a purulent yellow

TABLE 1. *Biochemical characteristics of 36 K. ozaenae isolates (one per patient)*

Characteristic	No. of strains	% Positive	Expected % positivity for *K. ozaenae*[b]	Expected % positivity for *K. pneumoniae*[b]
ONPG[a]	27	100	90	99
Arginine dihydrolase	26	23	23	0.2
Lysine decarboxylase	30	43	32	75
Ornithine decarboxylase	30	0	1	0.9
Citrate	30	33	40	95
Hydrogen sulfide	30	0	0	0
Urease	30	13	6.7	64
Tryptophane deaminase	26	0	0	0
Indole	26	0	0	19
Voges-Proskauer	26	0	0	92
Gelatin	26	4	0	0.2
Glucose	26	100	98	99
Mannitol	26	100	92	100
Inositol	27	56	61	97
Sorbitol	26	54	44	99
Rhamnose	27	74	67	98
Sucrose	26	35	21	100
Melibiose	26	92	83	100
Amygdalin	26	88	90	100
Arabinose	26	77	68	100
Nitrate	30	97	92	100
Motility	17	0	0	0
Oxidase	30	0	0	0
Malonate	9	11	6	93

[a] ONPG, *o*-Nitrophenyl-β-D-galactopyranoside.

[b] Expected percentages were adapted from the API 20E System data base (see text) and from the study by Ewing and Martin (6).

discharge from his left ear; the left tympanic membrane could not be visualized. The mastoids were not tender. The eyes appeared jaundiced. The liver was enlarged but was nontender, and an abdominal fluid wave was present. Results of the remainder of the examination were normal.

A chest X-ray was normal. The leukocyte count was 14,900/mm^3, and the hematocrit was 40%. Other laboratory data included the following (milligrams per deciliter): Na, 127; K, 3.5; Cl, 88; HCO_3, 20; bilirubin, 9.0; glucose, 340; creatinine, 1.4; and blood urea nitrogen (BUN), 21. Alkaline phosphatase was 375 IU, and serum glutamic oxalacetic transaminase (SGOT) was 180 U/liter. Urine analysis showed glucosuria and ketonuria, but no cells or protein were seen. A smear of the ear discharge contained many polymorphonuclear leukocytes and gram-negative bacilli.

On the second hospital day, the patient's temperature rose to 40.3°C. He was unresponsive and had developed a mild right-sided paralysis. A cerebral angiogram and examination of the spinal fluid were normal. X-rays showed a destructive left mastoiditis extending to the petrous bone. He was treated with intravenous chloramphenicol (4 g/day) and gentamicin (4.5 mg/k per day). *K. ozaenae* (serotype 5) was isolated from the discharge from the ear and two sets of blood cultures. The next day, the patient underwent a simple mastoidectomy. Purulent material obtained from the mastoid grew *K. ozaenae*. The subsequent hospital course was uneventful, and the patient fully recovered. The gentamicin was discontinued. Chloramphenicol therapy was continued for a total of 60 days.

Case 2 (bacteremia). A 19-year-old Mexican-American male was admitted to the UCLA Medical Center with acute myelomonocytic leukemia and was treated with 6-thioguanine, cytosine arabinoside, and daunomycin. With this therapy, a nearly aplastic marrow was obtained. There was no evidence of recovery of normal bone marrow elements on subsequent serial aspirates. The patient required repeated transfusions with packed erythrocytes, platelets, and leukocytes.

The patient developed a persistent fever while receiving cytotoxic medications. The source of the fever could not be determined despite multiple blood, urine, throat, and stool cultures. He was empirically treated with intravenous carbenicillin (30 g/day) and amikacin (1.5 g/day) or netilmicin (360 mg/day) for 47 days. Later, he was also treated with parenteral amphotericin B.

While receiving broad-spectrum antimicrobial therapy, the patient developed a perirectal fissure with surrounding cellulitis, but without abscess formation. Cultures of the fissure and cellulitis grew *K. ozaenae, Proteus rettgeri,* group D *Streptococcus,* and *Candida albicans.* Simultaneous stool cultures also grew *K. ozaenae,* but blood cultures taken at that time were negative. Blood cultures drawn 4 days later grew *K. ozaenae* (serotype 31). The same organism was isolated from three other sets of blood cultures drawn over the following 3-day period. The organism from all sites and at all times was resistant to ampicillin, cephalothin, tetracycline, tobramycin, kanamycin, gentamicin, and amikacin. It was susceptible to chloramphenicol. The patient deteriorated steadily and died despite carbenicillin, netilmicin, and amphotericin therapy; no autopsy was performed.

A total of 64 isolates of *K. ozaenae* were cultured from 36 patients during a 40-month period. Over 7,500 isolates of *K. pneumoniae* (approximately 210 per month) were recovered at the UCLA Medical Center during the same time period. *K. pneumoniae* were isolated most often from urine (38% of *K. pneumoniae* isolates)

TABLE 2. *Twelve patients with infections associated with K. ozaenae—summary of clinical and laboratory data*[a]

Case no.	Age (yr)	History	Physical examination	Pertinent laboratory data[a]	Cultures
Bacteremia					
1	52	Trauma to left ear, purulent otic discharge; fever, chills, malaise, and confusion	Purulent otic discharge, fever	Radiographic evidence of left mastoiditis	Otic discharge *Klebsiella ozaenae* *Corynebacterium* species *Staphylococcus epidermidis* Alpha-hemolytic streptococcus Mastoid (operative) *Klebsiella ozaenae* Blood *Klebsiella ozaenae*
2	19	Chronic anemia, acute myelomonocytic leukemia	Fever, perirectal fissure	Leukopenia	Rectal fissure *Klebsiella ozaenae* *Proteus rettgeri* *Candida albicans* *Staphylococcus epidermidis* Group D *Streptococcus* (enterococci) Stool *Candida albicans* *Klebsiella ozaenae* *Proteus rettgeri* *Staphylococcus epidermidis* Group D *Streptococcus* (enterococci) Blood *Klebsiella ozaenae*
Urinary tract infection					
3	19	Dysuria, urinary frequency, urgency	Normal	Urine: 10–12 WBC/hpf 2 RBC/hpf, moderate bacteriuria	Urine *Klebsiella ozaenae*, $>10^5$ CFU/ml
4	56	Hypertension, operative urinary catheterization	Fever	Urine: 1–2 WBC/hpf, moderate bacteriuria	Urine *Klebsiella ozaenae*, $>10^5$ CFU/ml *Klebsiella pneumoniae*, $>10^5$ CFU/ml
5	101	Arteriosclerotic heart disease, urinary retention	Fever, disorientation	Urine: 10–15 WBC/hpf	Urine *Klebsiella ozaenae*, $>10^5$ CFU/ml
Soft tissue infection					
6	16	Chondromalacia and chronic left patella subluxation; repaired with a left tibial bone graft	Postoperative wound infection (left knee and iliac crest donor site)	No radiographic evidence of osteomyelitis	Knee wound *Klebsiella ozaenae* *Staphylococcus epidermidis* *Corynebacterium* species
Mucopurulent nasal discharge					
7	56	Recurrent sialic duct stones; chronic postnasal discharge	Deviated nasal septum; purulent drainage from choanae; no atrophic changes	Radiographic evidence of bilateral frontal sinusitis	Nasal discharge *Klebsiella ozaenae* *Streptococcus pneumoniae* *Staphylococcus aureus* *Aspergillus* species
8	32	Chronic nasal bleeding and obstruction	Mucopurulent nasal discharge, no crusting or atrophic changes	None obtained	Throat *Klebsiella ozaenae* Viridans streptococci *Neisseria* species
9	32	Nasal discharge	Nasal discharge	Radiographic evidence of maxillary sinusitis	Nasal discharge *Klebsiella ozaenae* *Corynebacterium* species *Staphylococcus aureus*

TABLE 2—*Continued*

Case no.	Age (yr)	History	Physical examination	Pertinent laboratory data[a]	Cultures
10	32	Chronic nasal obstruction; weight loss, productive cough, hemoptysis	Atrophic rhinitis; blood crusting in posterior nasopharynx	Positive sputum for acid-fast bacilli; right upper lobe cavitation and bronchopneumonia	Sputum *Mycobacterium tuberculosis* *Klebsiella ozaenae* *Enterobacter cloacae* Viridans streptococci *Neisseria* species
Mucopurulent nasal discharge					
11	50	Chronic nasal congestion	Mucopurulent nasal discharge; no atrophic changes	Radiographic evidence of maxillary sinusitis	Nasal discharge *Klebsiella ozaenae* *Haemophilus influenzae* *Streptococcus pneumoniae* *Corynebacterium* species
12	32	Chronic rhinitis	Atrophic rhinitis	Nasal biopsy; atrophic rhinitis with metaplastic changes in the mucus glands	Nasopharynx *Klebsiella ozaenae* *Escherichia coli* *Streptococcus pneumoniae* Group B *Streptococcus*

[a] WBC, leukocytes; RBC, erythrocytes; hpf, high power field.

and sputum (23% of isolates).

K. ozaenae were isolated most frequently from sputum, always in mixed culture (Table 3). Eight of the 13 patients with sputum isolates had been hospitalized for 3 or more days before the sputum was cultured. There were, however, no clusters of infection or instances of apparent cross-infection. In only two patients was there radiographic evidence of a concurrent pneumonia. A transtracheal aspiration was not performed in these two individuals. *K. ozaenae* was not isolated from any of the 159 transtracheal aspirations processed in the Wadsworth Anaerobic Bacteriology Laboratory during the period of this study.

Isolation of *K. ozaenae* was associated with infection in 12 patients (33%). It was the primary pathogen in five patients (Tables 2 and 3).

Six patients had a mucopurulent nasal discharge associated with the isolation of *K. ozaenae* in mixed culture. All six were afebrile. A foul odor was not noted in any of these patients; two had documented atrophic rhinitis; three patients had radiographic evidence of paranasal sinusitis (Table 2).

Of the isolates tested, 26% were susceptible to ampicillin, 95% to cephalothin, and 90% to gentamicin (Table 4). The majority of strains resistant to kanamycin, tobramycin, amikacin, gentamicin, cephalothin, and ampicillin were isolated from patients who had been hospitalized for greater than 7 days or were receiving broad-spectrum antibiotics just before or at the time the organism was isolated (e.g., case 2).

TABLE 3. *Association of 64 isolates of Klebsiella ozaenae with infection*

Source	No. of isolates /no. of patients	Infection documented[a]	*K. ozaenae* the only pathogen present[a]
Blood	8/2	1, 2	1, 2
Ear or mastoid	2/1	1	1
Soft tissue	7/5	2, 6	6
Urine	6/5	3, 4, 5	3, 5
Nasopharynx	6/4	7, 9, 11, 12	—
Throat	4/3	8	—
Sputum	23/13	10	—
Stool	7/4	—	—
Vagina	1/1	—	—

[a] Numbers indicate case numbers; see Table 2. —, Isolate not associated with a documented infection.

DISCUSSION

K. ozaenae is an unusual clinical isolate; approximately two isolates per month have been identified at the UCLA Medical Center. Associated infection was present in one-third of the patients from whom the organism was isolated. *K. ozaenae* was the primary pathogen in 14% of the patients.

Our cases demonstrate the pathogenicity of *K. ozaenae* in otitis media, mastoiditis, bacteremia, urinary tract infection, and soft tissue infection. Berger et al. (1) have also reported the isolation of *K. ozaenae* from patients with bacteremia and soft tissue infection. Klipstein et al. (8) have isolated an enterotoxogenic strain of *K. ozaenae* from a jejunal aspirate of a patient with tropical sprue. Until recently, however, most investigators have noted its isolation only from the upper respiratory tract (2, 3, 7, 9, 11, 13). Fallon re-

TABLE 4. *Antimicrobial susceptibility of K. ozaenae by agar dilution method*[a]

Antibiotic	No. of isolates tested	No. of isolates susceptible	% Susceptible
Ampicillin	19	5	26
Tetracycline	14	3	21
Cephalothin	21	20	95
Chloramphenicol	3	3	100
Gentamicin	20	18	90
Kanamycin	8	7	88
Tobramycin	2	1	50
Amikacin	9	8	90

[a] Only one isolate per patient included.

peatedly isolated the organism in the sputum of patients with chronic bronchitis for as long as 3 years and isolated it from the sputum of five patients with primary pneumonia in whom there was no other apparent pathogen (13).

K. ozaenae was isolated most often from sputum in mixed cultures, but in none of our patients was it established as a cause of lower respiratory tract infection. We have never isolated the organism from a transtracheal aspirate, nor has this been reported elsewhere. Since *K. ozaenae* has been isolated from irrigation solutions, it may be a nosocomial colonizer (1). Although many of our patients had been hospitalized for at least 3 days before the isolation of *K. ozaenae,* at least 30% acquired the organism in the community.

K. ozaenae has been thought to be a possible pathogen exclusively in cases of ozena or atrophic rhinitis (12). Ozena is a chronic rhinitis characterized by atrophic changes in the nasal mucosa and turbinates, enlargement of the nasal passages, and a foul-smelling mucopurulent discharge which tends to dry into crusts (3, 13). Many theories as to the etiology of ozena have been proposed (including a bacterial cause), but none has been proven (2, 3, 13).

Six of our patients had a mucopurulent nasal discharge (cases 7 through 12), but none of them demonstrated all of the features of ozena. Case 12 had atrophic rhinitis with metaplastic changes of the mucus glands; upon biopsy, these changes are found characteristically in patients with ozena. Paranasal sinusitis has been described in association with ozena and was present in three of our patients. The cultures of all six patients with mucopurulent nasal discharge contained other bacteria also. We were unable to determine which, if any, were pathogenic and which were colonizers or components of the normal nasopharyngeal flora.

K. pneumoniae is the species most frequently isolated in clinical laboratories and is second to *Escherichia coli* among clinical isolates of gram-negative bacteria in our hospitals. Unlike *K. ozaenae, K. pneumoniae* is recovered more frequently from urine than sputum (4, 10). *K. ozaenae* has not been proven to cause pneumonia, whereas *K. pneumoniae* is known to cause a characteristic lobar pneumonia. The biochemical characteristics of *K. pneumoniae* and *K. ozaenae* are outlined in Table 1.

The majority of isolates of *K. pneumoniae* are resistant to ampicillin and carbenicillin but are susceptible to cephalothin and the aminoglycosides. Berger et al. (1) reported their isolates of *K. ozaenae* to be susceptible to ampicillin and carbenicillin and suggested that infections due to this organism might be successfully treated with these agents. The susceptibility of *Klebsiella* to carbenicillin has not been routinely determined at the UCLA Medical Center. Of our isolates tested, 73% were resistant to ampicillin. This pattern of resistance may be due to the prior exposure of many of our patients to antimicrobial therapy. One of our blood culture isolates was resistant to ampicillin, cephalothin, gentamicin, tobramycin, and amikacin. The infected patient (case 2) had received 6 weeks of antimicrobial therapy before the onset of bacteremia.

K. ozaenae can no longer be considered just a colonizer of the nasopharynx or a possible cause of ozena. It is a cause of community or nosocomially acquired infections of the urinary tract, soft tissue, middle ear, and blood.

The spectrum of disease caused by this organism is certainly more extensive than has been appreciated before this decade.

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